REMARKS

Claims 1-11 are currently pending in this application. Claims 3, 6, 7, and 11 have been amended herein to correct obvious typographical errors or to better define the claimed invention. Accordingly, no new matter has been added by these amendents.

New claims 15-27 have been added herein. Due to the fact that original claims 12-14 were renumbered as claims 9-11 in the Preliminary Amendment filed February 6, 2001, Applicants have identified claims 9-11 as "previously amended" and original claims 12-14 as "cancelled." Applicants have begun numbering the new claims with claim number 15 in order to avoid confusion. Support for these new claims is found in the original claims and in the specification at, *inter alia*, page 19, lines 21-32 and Table 1, page 22. Accordingly, no new matter has been added by the addition of these new claims.

Therefore, after entry of this amendment, claims 1-11 and 15-27 will be pending in the application.

Page 42 has been added to the specification. This page was inadvertently omitted from the instant application. However, the information contained in page 42 is present in the abandoned parent application U.S.S.N. 08/758,005, of which this application is a continuation application. Accordingly, no new matter has been added by this amendment.

Applicants note that the Information Disclosure Statement filed May 18, 2001, has not been considered. Applicants enclose herewith a Supplemental Information Disclosure Statement containing both the references listed in the Information Disclosure Statement filed May 18, 2001, as well as some additional references.

The outstanding rejections are addressed individually below.

1. ***Claims of the present invention are not unpatentable over claim 1 of U.S. Patent No. 5,591,721.***

Claims 1-11 stand rejected under the judicially created doctrine of obviouness-type double patenting as allegedly being unpatentable over claim 1 of U.S. Patent No. 5,591,721. Applicants respectfully traverse this rejection.

The present claims do not embrace the method of claim 1 of U.S. Patent No. 5,591,721 because the oligonucleotide used in this method requires "phosphorothioate internucleoside linkages between every nucleoside." The claims of the present invention require "at least one phosphorothioate internucleotide linkage and at least one internucleotide linkage selected from the group consisting of alkylphosphonate, phosphorodithioate, alkylphosphonothioate, phosphoramidate, phosphoramidite, phosphate ester, carbamate, carbonate, phosphate triester, acetamidate, and carboxymethyl ester." (emphasis added)

Accordingly, as Applicants submit that the claims of the present invention are not unpatentable over claim 1 of U.S. Patent No. 5,591,721, it is respectfully requested that this rejection be reconsidered and withdrawn.

2. ***Claims 1-11 are enabled.***

Claims 1-11 stand rejected under 35 U.S.C. § 112, first paragraph because the specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicants respectfully traverse this rejection.

M.P.E.P § 2164.01 states that 35 U.S.C. § 112, first paragraph, "has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation." (citation omitted). The same section further states that "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation."

The specification teaches one of skill in the art to how to make the invention (*see, e.g.*, the specification at page 17, line 4 to page 18, line 29 (which teaches the range of size, linkages, and modifications for the oligonucleotide); page 19, lines 8-15 (which teaches methods for preparing unmodified and modified oligonucleotides that are well known in the art); page 22, lines 27-36 (which describes chimeric oligonucleotides); Example 1, page 39, line 19 to page 41, line 21 (which teaches synthesis and analysis of oligonucleotides); and Example 2, page 41, line 23 to page 43, line 26(which teaches radioactive labeling of the oligonucleotides)).

Furthermore, the specification teaches one of skill in the art how to use the invention (*see, e.g.*, the specification at page 33, lines 4-34 (describing pharmaceutical formulations); page 34, lines 1-18 (describing dosage amounts), and Example 3, page 44, lines 3-12 (describing dosing in animals)).

Therefore, the specification has fully enabled the invention as claimed because it teaches how to make and use the invention without undue experimentation.

Furthermore, the specification provides examples indicating that the invention works as claimed.

The specification teaches that 2'-O-modified oligonucleotides, including 2'-O-alkyl oligonucleotides, have been introduced intact into the body following oral administration (page 34, line 24 to page 37, line 2; page 37, line 4 to page 38, line 18; page 38, lines 28-32; and page 39, lines 7-9).

The Office Action indicates at page 5 that "[n]o guidance is provided in the specification or in the published literature regarding successful operation of the claimed invention using any type of oligonucleotide other than an all-phosphorothioate oligonucleotide having at least two 2'-O-methyl ribonucleotides at each end." Applicants respectfully disagree with this statement.

For example, the specification indicates at page 35, lines 25-30 (describing Figure 3B), page 36, lines 13-18 (describing Figure 11B), and page 38, lines 9-18 (describing

Figure 12) that chimeric oligonucleotides were also tested. The preparation of the chimeric oligonucleotide is described in Example 1, page 41, lines 1-21.

In addition, Applicants enclose herewith the Declaration Under 37 C.F.R. §1.132 of Dr. Ruiwen Zhang, and copies of two references that corroborate the teachings of their specification. These references demonstrate that oligonucleotides comprising 2'-O-alkyl ribonucleotides are orally bioavailable.

The Declaration of Dr. Ruiwen Zhang provides *in vivo* data demonstrating an oligonucleotide with two 2'-O-methylribonucleotides at the 5' terminal end and four 2'-O-methylribonucleotides at the 3' terminal end was effective in decreasing tumor mass in nude mice when administered orally, and therefore, would have been present in intact form in plasma at least six hours following oral administration. The Declaration also provides *in vivo* data indicating that an oligonucleotide with four methylphosphonate linkages at both the 3' and 5' ends exhibit oral bioavailability and was present in intact form in plasma at least six hours following oral administration in the same animal models described as used in the specification. This data corroborates the teachings of the specification.

Additionally, a reference distributed on February 6-7, 1997, at the International Business Communications' Fourth Annual International Symposium on Oligonucleotide- & Gene Therapy-Based Antisense Therapeutics, San Diego, California (attached hereto as Appendix A), demonstrates that 2'-O-alkyl ribonucleotides, such as 2'-O-methyl, 2'-O-methoxyethyl, and 2'-O-propyl ribonucleotides, exhibit oral bioavailability. In addition, the reference distributed at the Nature Biotechnology Conference, *Antisense 97: Targeting the Molecular Basis of Disease*, May 1-2, 1997, held in Cambridge, Massachusetts (attached hereto as Appendix B) shows that 2'-O-methoxyethyl ribonucleotides exhibit increased stability and oral bioavailability. A 2'-O-methoxyethyl ribonucleotide is merely a substituted 2'-O-alkyl ribonucleotide.

Furthermore, as stated in M.P.E.P § 2164.03 "even in unpredictable arts, a disclosure of every operable species is not required." Applicants submit that this art is

no longer unpredictable. Additionally, even if some of the species in a genus claim are inoperative, the claims are not necessarily invalid. *Atlas Powder Co. v. E.I. Du Pont de Nemours & Co.*, 750 F.2d 1569, 1576; 224 U.S.P.Q. (BNA) 409. "It is not a function of the claims to specifically exclude...possible inoperative substances...." *Id. (citing In re Dinh-Nguyen*, 492 F.2d 856, 858-59, 181 U.S.P.Q. (BNA) 46, 48 (CCPA 1974) (emphasis omitted); *accord, In re Geerdes*, 491 F.2d 1260, 1265, 180 U.S.P.Q. (BNA) 789, 793 (CCPA 1974); *In re Anderson*, 471 F.2d 1237, 1242, 176 U.S.P.Q. (BNA) 331, 334-35 (CCPA 1973)). Furthermore, the specification describes in Examples 2-6 (page 41, line 23 to page 47, line 22) methods for radioactive labeling of oligonucleotides, administering them to animals, and determining whether the oligonucleotides are present in intact form in plasma at least six hours following oral administration. Thus, the specification teaches how to distinguish operable species from inoperative species.

Accordingly, Applicants respectfully submit that the specification fully enables the invention as claimed, and furthermore, the specification enables more embodiments than those admitted to be enabled in the Office Action.

The Office Action additionally states that the claims, given their broadest interpretation, "read on treating *any* disease via oral administration of an all phosphorothioate oligonucleotide having at least two 2'-O-methyl ribonucleotides at each end" (page 6).

Applicants' invention is not directed to methods for designing specific oligonucleotides effective for targeting specific genes. Nor is Applicants' invention directed to a method for predicting or achieving a particular phenotypic effect. Rather, Applicants' invention is the more basic method of *introducing into a mammal an oligonucleotide possessing certain recited structural features, whereby the oligonucleotide is present in intact form in plasma at least six hours following oral administration*. The effect of the oligonucleotide once it has been introduced intact into the mammal is not an element of the present claims.

Furthermore, the specification teaches that various effective antisense nucleotides have already been described for many different known viral nucleic acid sequences (*see, e.g.*, page 27, lines 3-18) and that nucleic acid sequences are known or have been described for other viruses and pathogenic organisms, to which antisense sequences could be made (page 27, lines 19-30 and page 28, line 28 to page 29, line 8). However, in the claims at issue, the particular nucleic acid sequence of the oligonucleotide administered is not an element. Rather, the claims are directed to oral delivery of the intact oligonucleotide.

However, Craig, et al. (*Exp. Opin. Ther. Patents* (1997) 7(10):1175-1182; attached hereto as Appendix C) teaches at page 1177 that once a modification to the oligonucleotide backbone "is found to confer a favorable characteristic, it can then be used in oligonucleotides having *different* sequences of nucleosides and, thus, provide utility for the treatment of other diseases" (emphasis added) as well as discussing information regarding the patentability of antisense technology.

The Office Action further alleges that "[m]ethods of targeting oligonucleotides into a subject (whole organism) fall into the broad area known as gene therapy methods. While delivery of nucleic acids in and of itself is not considered as therapy *per se*, delivery shares many of the obstacles recognized for the actual therapy methods because successful therapy methods are, for the most part, based on the ability to deliver exogenous nucleic acids to cells or tissues of interest" (page 6). Applicants respectfully disagree with this analogy, and submit that the concerns regarding delivery in gene therapy are not applicable to the claimed invention. As discussed above, Applicants' invention is a method for orally introducing into a mammal an intact oligonucleotide possessing certain recited structural features. The effect of the oligonucleotide once it has been introduced intact into the mammal is not an element of the present claims. The two independent claims require that the oligonucleotide is present in intact form in plasma at least six hours following oral administration. As described above, the specification indicates that these results have been achieved.

Applicants respectfully assert that the Examiner may be confusing the requirements under law for obtaining a patent with the requirements for obtaining government approval for marketing a particular drug for human consumption. *See In re Brana*, 51 F.3d 1560, 1567, 34 U.S.P.Q.2d (BNA) 1436 (Fed. Cir. 1995), citing *Scott v. Finney*, 34 F.3d 1058, 1063, 32 U.S.P.Q.2d (BNA) 115, 120 (Fed. Cir. 1994) ("Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) Proceedings" (emphasis added)). Determining effective parameters for orally administering to a mammal an oligonucleotide comprising the structural features recited in the claims, whereby the oligonucleotide is present in intact form in plasma at least six hours following oral administration would be considered a routine process by skilled artisans, and would not require undue experimentation.

Accordingly, Applicants respectfully request that this rejection under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

CONCLUSIONS

In view of the arguments set forth above, Applicants respectfully request reconsideration and reexamination of the above-referenced patent application. Applicants submit that the rejections contained in the Office Action mailed on October 8, 2002, have been overcome, and that the claims are in condition for allowance.

Applicants enclose herewith a Petition for a Three Month Extension of Time pursuant to 37 C.F.R. § 1.136, until April 8, 2003, to respond to the Examiner's Office Action mailed on October 8, 2003. Please charge our Deposit Account No. 08-0219 the $465.00 fee (small entity) for this purpose.

Applicants also submit herewith a Supplemental Information Disclosure Statement. Please charge our Deposit Account No. 08-0219 the $180.00 fee for this purpose.

Additional claim fees totaling $248.00 are believed to be due for the new claims added. Please charge our Deposit Account No. 08-0219 the $248.00 fee for this purpose.

No other fees are believed to be due in connection with this response. However, please charge any underpayments or credit any overpayments to Deposit Account No. 08-0219.

If the Examiner believes that any further discussion of this communication would be helpful, please contact the undersigned at the telephone number provided below.

Respectfully submitted,

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Date: 4/3/03

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